Amendments to the Specification:

Please replace the title of the application with the following:

"An Array of Toxicologically Relevant Canine Genes and Uses Thereof"

Please replace paragraph [0094] with the following amended paragraph:

[0094] Several techniques are well known to a skilled artisan for attaching a gene or a fragment thereof to a solid substrate such as a glass slide. One method is to attach an amine group, a derivative of an amine group, another group with a positive charge or another group which is reactive to one end of a primer that is used to amplify a gene or a gene fragment to be included in the array. Subsequent amplification of a PCR product will then incorporate this reactive group onto one end of the product. The amplified product is then contacted with a solid substrate, such as a glass slide, which is coated with an aldehyde or another reactive group which will form a covalent link with the reactive group that is on the amplified PCR product and become covalently attached to the glass slide. Other methods using amino propryl silicane surface chemistry are disclosed by Corning Company at ~~<http://www.cmt.corning.com.>~~ their website found on the world wide web at cmt.corning.com; other methods for making microarrays which are readily accessible are found ~~at~~ on ~~<http://cmgm.stanford.ecu/pbrownl>~~the world wide web at cmgm.stanford.ecu/pbrownl.

Amendments to the Claims:

The listing of claims will replace all prior versions, and listings of claims in the application:

Listing of Claims:

Claims 1-8 (cancelled)

Claims 9-11 (cancelled)

Claims 12-20 (cancelled)

Claims 21-23 (cancelled)

Claims 24-30 (cancelled)

Claims 31-39 (cancelled)

Claim 40. (cancelled)

Claim 41. (new) An array comprising a combination of toxicologically relevant canine nucleic acid molecules and fragments thereof comprising SEQ ID Nos.: 115-176, 179, 182, 185, 188, 191, 194, 197, 200, 203, 206, 209, 212, 213-384.

Claim 42. (new) The array according to claim 41 wherein the array contains a substrate for attaching toxicologically relevant canine nucleic acid molecules thereto.

Claim 43. (new) The array according to claim 42 wherein the substrate is glass.

Claim 44. (new) An array comprising a combination of toxicologically relevant canine nucleic acid molecules and fragments thereof comprising SEQ ID Nos.: 115, 118, 123, 124, 135, 137, 138, 141, 149, 165, 179, 188, 200, 255, 238.

Claim 45. (new) The array according to claim 47 wherein the array contains a substrate for attaching toxicologically relevant canine nucleic acid molecules thereto.

Claim 46. (new) The array according to claim 47 wherein the substrate is glass.

Claim 47. (new) An array comprising at least 10 nucleic acid molecules wherein the 10 nucleic acid molecules are SEQ. ID Nos.: 115-124.

Claim 48. (new) The array according to claim 44 wherein the array contains a substrate for attaching toxicologically relevant canine nucleic acid molecules thereto.

Claim 49. (new) The array according to claim 44 wherein the substrate is glass.

REMARKS/ARGUMENTS

Please cancel claims 1-40 and add new claims 41-49. New claims 41-49 are added to clarify the invention as described in the application. New claims 41-49 are not added for reasons of patentability. No new matter is added by the additional claims and entry of new claims 41-49 is respectfully requested.

Specification

The Examiner objects to the disclosure because it contains an embedded hyperlink and/or other form of browser-executable code.

Applicant has amended the specification to delete the embedded hyperlinks at page 28 paragraph [0094]. Paragraph [0094] now reads as follows:

[0094] Several techniques are well known to a skilled artisan for attaching a gene or a fragment thereof to a solid substrate such as a glass slide. One method is to attach an amine group, a derivative of an amine group, another group with a positive charge or another group which is reactive to one end of a primer that is used to amplify a gene or a gene fragment to be included in the array. Subsequent amplification of a PCR product will then incorporate this reactive group onto one end of the product. The amplified product is then contacted with a solid substrate, such as a glass slide, which is coated with an aldehyde or another reactive group which will form a covalent link with the reactive group that is on the amplified PCR product and become covalently attached to the glass slide. Other methods using amino propryl silicane surface chemistry are disclosed by Corning Company at their website found on the world wide web at cmt.corning.com; other methods for making microarrays which are readily accessible are found on the world wide web at cmgm.stanford.ecu/pbrownl.

In response to the Examiner's comments regarding the title of the invention, applicants have amended the title of the invention to read:

"An Array of Toxicologically Relevant Canine Genes and Uses Thereof"

Objection of Claim 30 under 35 USC § 112

The Examiner objects to Claim 30 under 37 CFR 1. 75(c), as being of "improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Both Claim 24 and 30 are directed to an array comprising at least 10 canine toxicological response genes or a portion thereof. Therefore, it does not appear that Claim 30 further limits Claim 24 in any meaningful manner."

Applicant has cancelled claims 24-30 rendering this objection moot.

Rejection of Claims 24-30 under 35 USC § 102 (b).

8. The Examiner rejects Claims 24-30 under 35 U.S.C. 102(b) as being anticipated by Brennan (US Pat. 5,474,796, December 12, 1995). The Examiner states that "the claims, as written, are directed to an array comprising at least 10 portions of genes immobilized on a substrate. The claims allow for any "portion" such that the claims do not require any length limitation on the size of the "portions." Brennan teaches a method for making arrays and a 10-mer array. In Example 3, the array contains oligonucleotides having 10 nucleotides each (10-mers)(col.9 lines 48-52). The array represents every possible permutation of the 10-mer oligonucleotide (col. 9, lines 52-55). The Examiner states that Brennan teaches designing a hybridization array on a glass plate (Col. 7, lines 20-25)(limitations of Claim 25-26). Brennan teaches the reactions at the functionalized binding site may involve a covalent bond (col. 2, lines 22-25)(limitations of Claim 27). With respect to Claim 28, the array of Brennan is capable of hybridizing to

nucleic acids and is capable of indicating a toxic response. It is noted that this functional language does not further provide any structure to the array limitations. Claim 29 is directed to specific agents expression. This language also fails to provide any structural limitations on the claimed array. Since Brennan teaches every possible 10-mer on a solid support, the array inherently comprises at least 10 portions of canine toxicological response genes, namely portions of SEQ ID NO: 115-124, immobilized on a substrate. Therefore, since Brennan teaches every limitation of the instant claims, Brennan anticipates the claimed invention."

Applicant respectfully disagrees with the Examiner as to the 102(b) rejection wherein the Examiner relies on the Brennan reference in point 8 of the office action mailed May 19, 2003. To anticipate claims, a single source must contain all of the elements of the claims. See Hybritech Inc. v. Monoclonal Antibodies Inc., 802 F.2d 1367, 1379 (Fed. Cir. 1986). To constitute an anticipatory reference, the prior art must contain an enabling disclosure. A reference contains an enabling disclosure when a person of ordinary skill could have combined the description of the invention in the prior art reference with his own knowledge of the art to have placed himself and thereby the public in possession of the invention. See Scripps Clinic & Research Found. v. Genetech, 927 F.2d 1565, 1578 (Fed Cir. 1991).

Brennan does not anticipate the claimed invention in that Brennan does not teach each element of the claims as presented. Brennan teaches a method for conducting a large number of chemical reactions on a support surface. Brennan teaches a method for "representing every possible permutation of the 10-mer oligonucleotide" (col. 9, lines 52-55). Synthesis of the oligonucelotide is carried out such that each oligonucleotide moving in a 5'-3' direction is identical to the preceeding element in nucleotide sequence except that it deletes the 5' most nucleotide, and adds a new 3'-most oligonucleotide (col. 9 lines 49-53).

Brennan does not teach or suggest providing cDNAs capable of hybridizing to nucleic acid targets that are indicative of a toxic response. Further Brennan does not identify which nucleic acid sequences to place on the array that would hybridize to toxicologically responsive nucleic acid sequences in the target.

A genus does not anticipate a species within the genus if one of ordinary skill would not have envisioned the claimed compound from the disclosed genus. The critical consideration in these situations most often revolves around the number of compounds embraced by the disclosed genus or sub-genus. See In re Petering, 301 F.2d 676, 682 (C.C.P.A. 1961).

Brennan discloses approximately 4^{10} (10-mer) sequences. It cannot reasonably be argued that one of ordinary skill would immediately envisage the toxicologically relevant sequences among the 4^{10} (10-mer) sequences disclosed by Brennan. Therefore, Brennan does not identify toxicologically relevant genes nor gene fragments either singly or in combination and placed on an array and used in identifying effects of toxic compounds on a subject and predicting agents that are toxic to a subject before causing observable histopathological damage.

Therefore, it is respectfully submitted that the new claims are not anticipated by Brennan.

Rejection of Claims 24-25, 28-30 under 35 USC § 103

The Examiner rejects Claims 24-25, 28-30 under 35 U.S.C. 103(a) "as being unpatentable over 1) Debouck et al. (Nature Genetics Supplement, Vol. 2, pages 48-50, January 1999) in view of 2a) Lillicrap et al. (US Pat. 6,251,632, June 2001) or 2b) Aguirre et al (US Pat. 6,201,114, March 2001) and in further view of 3) Pirson et al. (Genbank Accession Number X95367, October 1996) and 4) Yokota (Genbank Accession Number ABO08451, October 1997) and 5) Nakamura et al. (Genbank

Accession Number AB012918, October 1999) and 6) Van Leeuwen et al. (Genbank Accession Number L371 07, February 1997) and 7) Kobayashi et al. (Genbank Accession Number AB028042, November 1999) and 8) Somberg et al. (Genbank Accession Number U28141, June 1995) and 9) Kobayashi et al (Genbank Accession Number 084397, June 1999) and 10) Manning et al. (Genbank Accession Number L31625, April 1994) and 11) Puel et al. (Genbank Accession Number AF045016, February 1998) and 12) Ortiz-Garcia et al. (Genbank Accession Number AF021873, July 1999)."

The Examiner argues that "Debouck et al. (herein referred to as Debouck) teaches the use of DNA microarrays in drug discovery and development to measure expression patterns of thousands of genes in parallel (abstract). Debouck teaches DNA microarrays can be used for both genotyping and measuring mRNA levels to generate information rapidly for the identification and validation of novel therapeutic targets. Debouck teaches numerous benefits of microarrays which include the opportunity to compare the expression of thousands of genes between 'disease' and 'normal' tissues and cells to identify multiple potential targets; studying gene expression in disease models; investigating the mechanism of drug action by measuring the changes in mRNA levels before and after treatment with inhibitors; and monitoring expression of genes with toxicity potential. Debouck suggest that microarrays encompassing at least one element for each expressed gene in a gene organism will soon become available for many organisms (page 50, col. 2)."

The Examiner further states that "Debouck does not specifically teach canine expression genes on an array. However, Lillicrap et al. (herein referred to as Lillicrap) teaches the canine gene for factor VIII. Lillicrap teaches that dogs have been of increasing interest as a canine model system for studying of the physiology of human diseases characterized by factor VIII deficiencies such as hemophilia A. Lillicrap also teaches that the canine has shown promise as a model system for the development of methods of detecting and treating such diseases in humans (col. 4, lines 18-27). Lillicrap teaches methods for detecting expression of the factor VIII gene in canine tissue may be

performed by northern blot analysis. Specifically, Lillicrap teaches that bleeding disorders are believed to be due to significantly lower levels of factor VIII gene expression when compared to a "standard" factor VIII gene expression level (col. 20, lines 45-65). Therefore, Lillicrap teaches a method which comprises obtaining a sample of tissue from a canine, assaying for expression in the sample, and comparing the expression level to a standard sample. Therefore, Lillicrap teaches methods of assaying for canine expression levels."

Further the Examiner states that "Aguirre et al. (herein referred to as Aguirre) also teaches a canine gene, RPE65, which contains a mutation which affects dogs with congenital stationary night blindness (abstract). Aguirre contemplates assaying for the allele using an array. Moreover, each gene required by the claims was known in the art at the time the invention was made."

"Pirson et al. (Genbank Accession Number X95367, October 1996) teaches the c-myc proto-oncogene from canis familiaris, namely SEQ ID NO: 115. The nucleic acids of Pirson and SEQ ID NO: 115 are 100% identical."

"Yokota (Genbank Accession Number ABO08451 , October 1997) teaches the erbB-2 mRNA from canis familiaris, namely SEQ ID NO: 116. The nucleic acids of Yokota and SEQ ID NO: 116 are 100% identical."

"Nakamura et al. (Genbank Accession Number AB012918, October 1999) teaches the mRNA for catalase from canis familiaris, namely SEQ ID NO: 117. The nucleic acids of Nakamura and SEQ ID NO: 117 are 100% identical."

"Van Leeuwen et al. (Genbank Accession Number L371 07, February 1997) teaches the mRNA from p53 from canis familiaris, namely SEQ ID NO: 118. The nucleic acids of Van Leeuwen and SEQ ID NO: 118 are 100% identical."

"Kobayashi et al. (Genbank Accession Number AB028042, November 1999) teaches the mRNA from metallothionein isoform 2 (mt-il gene) from canis familiaris, namely SEQ ID NO: 119. The nucleic acids of Kobayashi and SEQ ID NO: 119 are 100% identical."

"Somberg et al. (Genbank Accession Number U28141, June 1995) teaches the mRNA from interleukin-2 from canis familiaris, namely SEQ ID NO: 120. The nucleic acids of Somberg and SEQ ID NO: 120 are 100% identical."

"Kobayashi et al (Genbank Accession Number 084397, June 1999) teaches the mRNA for metallothionein-1 from canis familiaris, namely SEQ ID NO: 121. The nucleic acids of Kobayashi and SEQ ID NO: 121 are 100% identical."

"Manning et al. (Genbank Accession Number L31625, April 1994) teaches mRNA from intercellular adhesion molecule -1 from canis familiaris, namely SEQ ID NO: 122. The nucleic acids of Manning and SEQ ID NO: 122 are 100% identical."

"Puel et al. (Genbank Accession Number AF045016, February 1998) teaches the mRNA from MOR1 from canis familiaris, namely SEQ ID NO: 123. The nucleic acids of Puel and SEQ ID NO: 123 are 100% identical."

"Ortiz-Garcia et al. (Genbank Accession Number AF021873, July 1999) teaches mRNA from beta-actin from canis familiaris, namely SEQ ID NO: 124. The nucleic acids of Oritz-Garcia and SEQ ID NO: 124 are 100% identical."

The Examiner states that "it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the gene expression array of Debouck to comprises canine genes which were known at the time the invention was made. Debouck teaches that microarrays may be used for both genotyping and gene analysis. The art provides numerous genes from canines which are known to be affected

by expression levels and alterations. Therefore, to place canine genes upon arrays to enable simultaneous analysis of a multitude of genes in parallel would have the expected benefit of high throughput analysis. Debouck teaches numerous reasons why analyzing genes on an array is useful. Among these reasons is to study gene expression and toxicological effects of various compounds on gene expressions."

"The instant claims are drawn to ten canine toxicological response genes which were known at the time of filing. All of these genes are available within the same database, namely Genbank. Placing these well-known canine genes, including c-myc, p53, MOR1, betaactin, upon an array would have been obvious to the ordinary artisan at the time the invention was made. Moreover, the art clearly suggests that canines may be used a model systems for human diseases. Therefore, placing the instantly claimed genes upon an array would facilitate gene expression of canine nucleic acids which would allow toxicological studies that would be useful for analyzing the model system of the canine which is taught to be of interest for analyzing the human."

Applicant respectfully disagrees with Examiner's 103 rejection of claims 24-25 and 28-30. For references to be combined, there must be some suggestion, motivation or teaching in the prior art that would have lead a person of ordinary skill in the art to select the references and combine them in the way that would produce the claimed invention. Where the prior art does not teach the same utility asserted for the claimed compound, the expectation for the compounds to have similar properties may not arise, and the motivation to combine the references would dissipate. The references cited by the Examiner for VIII gene suggest the gene useful for diagnosis of hemophilia, a blood disorder, for RPE65 gene, the reference suggests the gene is useful for identifying congenital stationary night blindness in dogs, for cmyc gene, the reference suggests the gene is a proto-oncogene. In addition, there is no motivation to combine these genes on an array given their distinctly different utilities as described in the disclosures. Further, there is no expectation of success for creating a toxicologically predictive array when,

before the applicant's disclosure, there was no suggestion that the identified genes were responsive to toxicological compounds.

It is improper in determining whether a person of ordinary skill would have been led to this combination of references, simply to use that which the inventor taught against its teacher. See W.L. Gore v. Garlock, Inc., 721 F.2d 1540, 1553 (Fed. Cir. 1983).

The genes associated with SEQ ID NO: 115-124 while known when the instant application was filed, were not described to be predictive of toxicity either on their own or in combination with other genes. The utility of the genes in SEQ ID NO: 115-124 as predictive of toxicity is taught by the present application. Using an applicant's disclosure as a blueprint to reconstruct the claimed invention from isolated pieces of the prior art contravenes the statutory mandate of §103 which requires judging obviousness at the point in time when the invention was made. See Grain Processing Corp. v. American Maize-Prods. Co., 840 F 2d. 902, 907 (Fed. Cir. 1988).

Therefore, the claims as written are not obvious in light of Debouck when combined with the twelve (12) other references. For the same reasons, this rejection does not apply to new claims 41-49.

Applicant respectfully requests that a timely Notice of Allowance be issued in this case. Should any further questions arise concerning this application, the Examiner is invited to call applicant's attorney at the number listed below.

John K. Abokhair
Tel.: (703) 391-2900
or
Janeen Vilven-Doggett
Tel.: (505)-922-1400

Respectfully Submitted,

ROBERTS ABOKHAIR & MARDULA, LLC

By_____

John K. Abokhair, Esq.
Reg. No. 30,537
Tel.: (703) 391-2900